and higher codes representing those values indicative of obstructive disease. Scores of 45 to 55 were considered consistent with a normal profile when all five coded values were between 9 and 11, and consistent with an undifferentiated profile when a mathematical balance of codes under, equal to, and over 10 resulted in a score of 45 to 55. Scores under 45 were assumed to represent restrictive profiles and scores over 55 to represent obstructive profiles. Forty-three percent of the population had normal lung function profiles, and 26.5 percent had undifferentiated lung profiles. The remainder was divided relatively evenly between the restrictive and obstructive lung profiles, with 14.9 percent having a restrictive defect and 14.3 percent having an obstructive picture. In Table 13 are revealed the results in smokers and nonsmokers, stratified by increasing asbestos exposure category. The data seem to suggest that neither obstructive nor restrictive lung disease occurs in nonsmoking asbestos workers and that restrictive and obstructive lung disease occur with equal frequency in asbestos miners who smoke. In addition, it appears that there is, if anything, a negative dose–response relationship between restrictive lung disease and increasing cumulative asbestos exposure. These results are particularly remarkable in the face of data from the same group of workers presented earlier in this section, which show a relatively clear dose–response relationship between cumulative asbestos exposure and decline in TLC and FEV_1 in both smokers and nonsmokers. The authors have interpreted this data to suggest that an association between smoking habit and the development of asbestos-related fibrosis may exist and that asbestos workers who smoke may develop either obstructive or restrictive lung disease. The inconsistencies between the data on pattern pulmonary function tests and the measures of individual test responses described earlier may be explained by the effects of changes in lung volumes on some of the measurements used to code the lung function profile. $FEV_{75\%}$ and $MMEF_{25-75\%}$ are measurements that, when reduced, are used in this coding scheme to define an individual as being obstructed. Both of these are measurements of airflow obstruction in the presence of normal lung volumes, but may also be reduced in the presence of diminished lung volumes secondary to restrictive lung disease. Indeed, examination of the pattern of pulmonary function response in nonsmoking asbestos miners (Figure 10) reveals that with increasing cumulative asbestos exposure, the decline in TLC in these workers was accompanied by a decline in $FEV_{75\%}$ and $MMEF_{25-75\%}$. This pattern, consistent with progressive restrictive lung disease, would define the worker by the coding scheme as having obstruction, or would counterbalance those scores for a restrictive category, thereby placing the worker in the undifferentiated category. A similar effect would occur in asbestos miners who smoke. As can be seen in Figure 10, the decline in FEV_1,

TABLE 12.—Coding of lung function profile

Code	Volumes (RV, TLC)	Flow rates (FEV$_{75\%}$ MMF)	(FEV$_1$/FVC)% percent predicted
7	<70	>130	>116
8	70–79	121–130	111–115
9	80–89	111–120	110–106
10	90–110	90–110	95–105
11	111–120	80–89	90–94
12	121–130	70–79	85–89
13	>130	<70	<84

FEV$_{75\%}$, and MMEF$_{25-75\%}$ is greater in smoking asbestos miners than in nonsmoking miners. This pattern, which is consistent with a combination of restriction and obstruction in these workers, would result in a progressive increase in the coding scheme obstructive score, and therefore may account for the absence of a dose–response relationship between asbestos exposure and restrictive lung disease in the asbestos workers who smoke. With increasing severity of restrictive lung disease, more and more workers would be categorized as having an obstructive or undifferentiated pattern and thus would drop out of the restrictive category.

A similar approach was taken by Muldoon and Turner-Warwick (1972), who categorized the lung function results in a consecutive series of 75 subjects with a history of exposure to asbestos who were referred to the Pneumoconiosis Medical Panel of London. The researchers categorized workers as having obstructive, restrictive, mixed, or normal lung function. They reported that the workers with obstruction did not have heavier smoking histories than the subjects with restrictive or normal lung function. However, examination of the data presented in their report reveals that, although the percentage of current smokers in the obstructive and restrictive groups was somewhat similar, there were marked differences in the frequency of former smokers. Indeed, all of the workers who had obstructive disease had a history of cigarette smoking. There were 13 workers in the group; 8 were current cigarette smokers and 5 were former cigarette smokers, of whom 3 had stopped smoking less than 1 year prior to the study. Of the entire group examined, there were only four workers who had never smoked cigarettes, and all of these workers fell into the restrictive category.

Murphy and colleagues (1972, 1978) also attempted to answer the question whether an increased prevalence of obstructive lung disease occurs in asbestos workers. They examined a group of 101 shipyard

TABLE 13.–Effects of chrysotile exposure on the health of 1,015 current Quebec asbestos workers

Dust index [1]	< 10	10–99	100–199	200–399	400–799	≥ 800
		Nonsmokers				
Prevalence percent [2]						
Chronic bronchitis	10	19	19	46	21	49
Dyspnea	0	19	24	31	13	44
Function profile– [3]						
prevalence percent						
Restrictive	3	3	3	1	1	1
Obstructive	0	1	0			
Percentage fall in function [2]						
VC	0	-10	-16	-18	-19	-23
FEV_1	0	-9	-9	-13	-15	-22
$DLCO_{ss}$, rest	0	-11	-15	-18	-12	-15
$DLCO_{ss}$, exercise	0	-8	-9	-18	-18	-20
		Smokers				
Prevalence percent [2]						
Chronic bronchitis	23	22	30	29	46	45
Dyspnea	4	15	18	21	30	32
Function profile– [3]						
prevalence percent						
Restrictive	8	14	16	10	4	13
Obstructive	12	12	13	12	23	12
Percentage fall in function [2]						
VC	0	-3	-7	-10	-13	-14
FEV_1	0	-3	-8	-10	-15	-15
$DLCO_{ss}$, rest	0	+4	+3	+5	-3	0
$DLCO_{ss}$, exercise	0	0	-2	0	-5	-7

NOTE: For all measurements, prevalence percent has been age-standardized to the total working population as of October 31, 1966. This was to allow for the smaller of number of men for whom function profiles were analyzed.
[1] Expressed in million particles per cubic foot years. [3]
[2] Based on a total sample of 1,015 men. [1]
[3] Based on 995 men. [2]
SOURCE: Becklake et al. (1976).

pipe coverers and compared them with 95 control subjects. The prevalence of smoking in these two populations was approximately the same. There were significant differences between the asbestos-exposed workers and the control population in vital capacity and FEV_1 in measurements taken both in 1966 and in 1972. However, there was no difference between the two groups in FEV_1 as a percent of FVC at either time point. In 1972, there was a significant difference between the two groups in the reported symptom of wheezing apart from colds. When this symptom was combined with the prevalence of an abnormal $FEV_1/FVC\%$, using the criteria of Ferris and Anderson (1962) for obstructive lung disease, the asbestos workers had a significant higher prevalence of obstructive lung disease in comparison with the control population. However, this

increased prevalence resulted from their reported symptoms and not from differences in measured pulmonary function.

In summary, lung function has been examined in several populations of smoking and nonsmoking asbestos workers. In populations of nonsmoking asbestos workers, a dose-related decline in TLC and a decline in FEV_1 and in $FEF_{25-75\%}$ consistent with the decline in TLC can be identified, a pattern consistent with a primarily restrictive lung function profile. In populations of cigarette-smoking asbestos workers, the decline in TLC is somewhat less than in nonsmoking asbestos workers and the decline in FEV_1 and $FEF_{25-75\%}$ is somewhat more. The percentage decline in FEV_1 compared with the percentage decline in FVC is greater in smoking asbestos workers, but not in nonsmoking asbestos workers. When smoking asbestos workers are compared with control populations with similar smoking habits, there is a significantly greater decline in FVC and TLC, but the ratio of FEV_1 to FVC is similar in the asbestos-exposed and the non-asbestos-exposed populations. The data are therefore consistent with independent effects of asbestos and cigarette smoking on lung function. This issue has been examined statistically by Samet and colleagues (1979) and by Rossiter and Weill (1974); an additive effect of smoking and asbestos exposure on the FVC was present, but there was no statistically demonstrable synergism.

Regan and colleagues (1971) evaluated the relative power of 16 clinical-radiological-pulmonary function variables in evaluating asbestosis and chronic airway disease. A decreased diffusing capacity for carbon monoxide (DLCO) and a decrease in the vital capacity had the greatest power to measure the severity of either obstructive or restrictive lung disease in workers with both smoking and asbestos exposure, but had little ability to distinguish between the two processes. The best indicator for distinguishing between restrictive lung disease and obstructive airway disease was FEV_1 as a percentage of the vital capacity. This variable had a better ability to distinguish between obstructive and restrictive disease than either the clinical or the chest roentgenogram findings or other tests of pulmonary function.

The absence of an effect of asbestos exposure on $FEV_1/FVC\%$ must be interpreted with caution. Although this test is the best measure of the presence of airflow obstruction in the presence of restrictive lung disease, it is not sensitive to changes in the small airways. Because both cigarette smoking and asbestos exposure have been shown to result in changes in the small airways of the lung, it is important to examine the effects of these two exposures on tests of small airway function.

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Small Airways Function

Airways in the lung with diameters of 2 mm or less are considered small airways and consist of bronchioles and respiratory bronchioles (airways with both nonrespiratory epithelium and alveoli in their walls). Considerable obstruction can be present in these airways without significantly altering the airway resistance or lung mechanics. In addition, abnormalities in the small airways are a prominent part of the abnormality present in chronic obstructive lung disease (COLD). The relationship of cigarette smoking to abnormalities in tests of small airways function, and of pathologic abnormalities of the small airways to functional changes, was reviewed in a previous Report of the Surgeon General (US DHHS 1984). Changes in the small airways of cigarette smokers may occur within the first few years of smoking, are more prevalent in heavy smokers, and increase in frequency with increasing duration of the smoking habit. Because the small airways are also involved in people who develop cigarette-induced COLD, tests of small airways function are usually abnormal in people with chronic airflow obstruction on conventional spirometry; however, it is not yet clear whether the early and reversible inflammatory changes in the small airways of smokers are the first stage in the pathophysiologic process of developing COLD or are merely a nonspecific irritant response to smoke that does not predispose to the development of COLD.

The response of the lung to asbestos also involves the small airways, and there has been considerable interest in functional changes of the small airways of asbestos workers. Relevant questions are these: Does asbestos cause changes in the small airways independent of smoking? Do the morphologic changes in the small airways caused by smoking differ from those caused by asbestos? Do the changes in the small airways of asbestos workers progress to airflow obstruction, as measured by standard spirometry, independent of cigarette smoking?

Woolcock and colleagues (1969) demonstrated that a group of bronchitic subjects with normal lung volumes and flow rates had abnormal tests of small airways function. Cosio and colleagues (1978) and Berend and colleagues (1979) were able to correlate abnormalities of tests of small airways function with morphologic changes in the small airways. The morphologic changes consisted of a respiratory bronchiolitis with goblet cell metaplasia, inflammation of the bronchiolar wall, smooth muscle hypertrophy, peribronchiolar fibrosis, and pigmentation of the bronchiole. Tests of small airways function (closing capacity and slope of the single breath nitrogen washout) were abnormal, with lower degrees of pathologic change; however, abnormalities on spirometric testing (FEV_1/FVC and $FEF_{25-75\%}$) were also correlated with more severe morphologic changes in the small airways.

The changes in the small airways of asbestos workers have been examined (Wright and Churg 1984; Churg and Wright 1984), and differences in the pattern of injury from that produced by cigarette smoking alone were identified. The researchers examined lung sections from 15 patients who had been exposed to asbestos and had abnormalities of the respiratory bronchioles, and compared these individuals with 15 control subjects matched for age, sex, and smoking status. Almost all of the subjects smoked (13 of 15), so it was not possible to examine the differences between smoking and nonsmoking asbestos workers or to rule out an interaction between smoking and asbestos. However, two distinct patterns seem to emerge. Churg and Wright found changes in the membranous bronchioles of the cigarette-smoking controls similar to those found by others (Cosio et al. 1978; Berend et al. 1979), including inflammation, pigmentation, and periobronchiolar fibrosis. The changes in the membranous bronchioles of the asbestos workers (almost all of whom were smokers) were qualitatively identical to those in the non-asbestos-exposed smokers; but quantitatively, the degree of fibrosis, the amount of pigmentation, and the percentage of membranous bronchioles involved was greater in the asbestos-exposed individuals. In the asbestos-exposed group, 67 percent of the membranous bronchioles showed marked fibrosis in comparison with 19 percent in the control population of smokers. The clearest distinction and the most diagnostically useful lesions occurred in the respiratory bronchioles and alveolar ducts. Forty-eight percent of the respiratory bronchioles and 35 percent of the alveolar ducts showed marked fibrosis in the asbestos-exposed group in contrast to 4 percent of the respiratory bronchioles and 0 percent of the alveolar ducts in the control population. These data suggest that cigarette smoking produces an inflammatory response with only modest amounts of fibrosis in the membranous bronchioles, and that the addition of asbestos exposure results in a marked increase in the fibrosis around the membranous bronchioles and an extension of this fibrosis to the respiratory bronchioles and alveolar ducts. Because there were so few nonsmokers examined in this study, the questions whether asbestos exposure alone causes an inflammatory response and whether the fibrotic lesions characteristic of asbestos exposure are influenced by smoking could not be addressed.

Given this description of the pathologic response of the small airways to cigarette smoke and asbestos dust, examination of the physiologic testing of the small airways in asbestos workers should focus on several questions: Does asbestos exposure alter the function of the small airways in people who have never smoked? Does this alteration in small airways function result in reductions in the rate of expiratory airflow (as occurs in cigarette smokers) independent of the reductions in lung volume that occur secondary to asbestos

exposure? (The increased resistance in the small airways may be compensated for by an increased elastic recoil of the lung available to drive expiratory airflow.) Does asbestos exposure increase the prevalence of abnormalities on tests of small airways function above that expected from smoking alone?

A number of researchers have examined small airways function in asbestos workers. Jodoin and colleagues (1971) examined 24 workers with normal chest roentgenograms whose asbestos exposure ranged from 6 months to 24 years. Two groups with comparable age and smoking prevalence, but with differing exposure to asbestos dust, were defined among those 24 workers. The more heavily exposed group had a 30 percent increase in lung static recoil pressure and had reduced rates of expiratory airflow for any given transpulmonary pressure, suggesting increased resistance in the small airways. This increased resistance did not result in obstruction on spirometric testing, as both $FEV_1/FVC\%$ and FEF_{25-75} actually increased in the workers with heavier asbestos exposure. In five of the subjects with heavier exposure, but with a normal FEV_1 and $FEV_1/FVC\%$, the maximal expiratory flow was reduced throughout the entire range of lung volume despite an increased driving pressure, suggesting that the degree of small airway obstruction was greater than the degree of increase in driving pressure. However, all five of the subjects were cigarette smokers; therefore, the reduced airflow could not be identified as due to the asbestos. The authors provided no separate analysis of the data for the nonsmokers in the study.

Several other authors (Harless et al. 1978; Cohen et al. 1984; Rodriguez-Roisin et al. 1980; Siracusa et al. 1983) have also presented evidence suggesting that asbestos exposure results in small airway dysfunction; however, the data on nonsmokers were not presented in a manner to allow evaluation as a separate group, or included ex-smokers with never smokers, making interpretation difficult.

Begin and colleagues (1983) examined airways function in 17 lifetime nonsmoking asbestos workers with an average of 28 years of exposure in the asbestos mines and mills of Quebec. Seven workers met the diagnostic criteria for asbestosis and 10 did not; none of the workers met the diagnostic criteria for chronic bronchitis, emphysema, or asthma. The lifetime nonsmokers without asbestosis had relatively normal lung function, but there was a slightly lower maximal expiratory flow at 25 percent of the vital capacity and a significantly elevated isoflow volume, suggesting dysfunction in the small airways. The seven workers with asbestosis had clear evidence of small airway obstruction with a threefold or fourfold increase in upstream resistance at low lung volumes. These data were supported by histologic evidence of peripheral airway obstruction and narrowing on lung biopsies in three of these men. However, this obstruction

in the small airways was not severe enough to significantly reduce the usual spirometric parameters of airflow obstruction, and none of these men had a significant reduction in $FEV_1/FVC\%$. The authors attributed this phenomenon to the higher pressures available to drive airflow in these workers with restrictive lung disease.

Cohen and colleagues (1984) attempted to examine the relationship of smoking and asbestos exposure in a cross-sectional study of a group of asbestos litigants. Unfortunately, ex-smokers were included with the group of nonsmokers. This results in an increasing prevalence of ex-smokers with increasing age, and ex-smokers have reduced lung function (US DHHS 1984); correspondingly, with increasing duration of asbestos exposure, there would also be an increasing prevalence of ex-smokers. This confounding of their exposure data makes meaningful interpretation impossible.

In summary, the evidence suggests that asbestos exposure can result in small airways dysfunction in nonsmoking workers, but this small airways dysfunction does not result in obstruction on standard spirometric testing. $FEV_1/FVC\%$ remains normal in these nonsmoking asbestos workers even in the presence of substantial increases in the airway resistance at low lung volumes and decreases in TLC. This picture differs from that in small airway dysfunction in cigarette smokers, where there is a decline in the $FEV_1/FVC\%$. This difference may be accounted for by the differences in elastic recoil pressure of the lung produced by these two injuries. Asbestos exposure results in increased elastic recoil of the lung, which provides an increased driving pressure that compensates for the increased resistance in the small airways. Thus, the rate of expiratory airflow is preserved. In contrast, the elastic recoil either remains normal or frequently decreases (in emphysema) with cigarette-induced lung injury, and therefore there is no compensatory increase in driving pressure to maintain the rate of expiratory airflow in the presence of an increased resistance in the small airways. In combined exposure to cigarette smoke and asbestos, the largely inflammatory response in the small airways due to smoking may occur conjointly with the largely fibrotic response in the same airways due to asbestos, and the resultant increase in the resistance in the small airways may be large enough to reduce expiratory airflow even in the presence of an increased elastic recoil.

In conclusion, asbestos exposure can result in reduced lung volumes in both smoking and nonsmoking workers, and may result in small airway dysfunction. However, the evidence does not suggest that airflow obstruction, as measured by a reduced FEV_1/FVC, is a result of asbestos exposure in nonsmoking asbestos workers or that it is worse than would be expected from the smoking habits of asbestos workers who smoke.

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Chest Roentgenographic Changes

One of the hallmarks of interstitial fibrosis due to asbestos is an abnormal chest roentgenogram, and despite the fact that biopsy-proven disease may be present with a normal roentgenogram (Epler et al. 1978), the x ray commonly reflects both the presence and the extent of fibrosis. Occasionally, particularly in early asbestos-induced lung disease, the chest roentgenogram may not be abnormal and the only abnormalities may be a reduced diffusing capacity or decreased lung volumes. The chest roentgenogram is less frequently abnormal in cigarette-induced chronic obstructive lung disease, but roentgenographic abnormalities can occur, particularly in advanced disease or when extensive emphysema is present. The abnormalities produced by these two processes are usually quite different on chest roentgenogram once the disease process is sufficiently advanced, and confusion about the roentgenographic diagnosis in severe disease is unusual.

The radiographic changes associated with asbestos include small irregular opacities, which commonly begin as a reticular pattern in the lower lung fields and may progress to diffuse interstitial densities throughout the entire lung with reduced lung volumes (Selikoff and Lee 1978; Fraser and Pare 1979). The abnormalities that have been reported with COLD include overinflation, prominence of lung markings ("dirty lungs"), tubular shadows, and in the presence of significant emphysema, oligemia, and bullae (Fraser and Pare 1979).

Roentgenographic Changes in Non-Asbestos-Exposed Populations

The literature establishing asbestos as a cause of interstitial fibrosis is extensive, and no significant scientific debate remains over the potential for occupational asbestos exposure to result in interstitial fibrosis; substantial numbers of asbestos workers have developed interstitial fibrosis as a direct consequence of their inhalation of asbestos dust. A review of this evidence is beyond the scope of this chapter and can be found elsewhere (Selikoff and Lee 1978). The questions raised by the combination of cigarette smoking and asbestos exposure do not include whether cigarette smoking is an independent competing cause of the extensive fibrotic process found in many workers following prolonged heavy exposure to asbestos. Cigarette smoking has not been shown to independently cause this kind of reaction in the lung. Therefore, this section focuses on three questions concerning the relationship of cigarette smoking to the roentgenographic changes caused by asbestos. In the absence of asbestos exposure, are the chest roentgenograms of cigarette smokers more likely to be interpreted as positive for interstitial fibrosis than those of nonsmokers? Do cigarette-smoking asbestos workers

have a higher prevalence of chest roentgenograms interpreted as positive for interstitial fibrosis than nonsmoking asbestos workers? Do cigarette-smoking asbestos workers have more severe interstitial fibrosis on chest roentgenograms than nonsmoking asbestos workers for comparable asbestos exposures?

The determination of whether radiologic findings consistent with interstitial fibrosis are present is part of the standard clinical interpretation of the chest roentgenogram. However, the International Labour Office (ILO) (1980) developed a classification by which the roentogenographic changes of pneumonconiosis can be measured and reported in a standardized way. Small opacities are characterized as rounded or irregular, and the profusion of the opacities is also described and quantitated on a numerical scale (from 0/0 to 3/4). This classification was designed as a descriptive rather than a clinical tool; as such, it is structured to be sensitive to the earliest roentgenographic changes. This sensitivity allows the investigation of early or mild disease, but also may reduce specificity. Using this classification, other mild, but not pneumoconiotic, disease in the general population may be interpreted as positive. Indeed, given the variety of causes of interstitial fibrosis other than inhalation of inorganic dust, the absence of any false positives by this classification would be surprising, and therefore the questions are the magnitude of this false positive rate and whether cigarette smoking influences that rate.

The semiquantitative ILO classification system can have substantial variability of interpretation, particularly at the lower levels of abnormality (Werner 1980). Table 14 shows the differences between the highest and lowest categorizations of 32,695 chest roentgenograms interpreted according to the ILO classification by three different readers as part of a study of asbestos-related disease. In general, there was good agreement, but in a number of cases marked differences of interpretations occurred, including the same radiographs being interpreted by different readers as negative (0/0) and as substantially positive (2/2). Werner discussed some of the problems generated by these differences in interpretation and offered some potential remedies, but the data pointed out that a system designed to be sensitive to low levels of abnormality may be expected to have a some variability of classification, particularly around the threshold of abnormality.

Weiss (1967, 1969) published a pair of studies evaluating the prevalence of a roentgenographic interpretation of interstitial fibrosis in smokers and nonsmokers drawn from the general population. The first study involved the examination of 70 mm chest photofluorograms of 999 men and women who came consecutively to the central survey unit of the Philadelphia Tuberculosis and Health Association. The films were evaluated for increased bronchovascular

TABLE 14.—Analysis of x rays of asbestos workers, lowest readings by highest readings (ILO U/C scale)

Lowest reading	Highest reading												Total
	0/-	0/0	0/1	1/0	1/1	1/2	2/1	2/2	2/3	3/2	3/3	3/4	
0/-	2	857	94	47	56	15	2	6	2		2		1083
0/0		20449	3406	2162	2699	693	153	283	47		18		29910
0/1			46	149	385	152	39	85	12	1	2		871
1/0				29	189	100	43	69	10	1	2		443
1/1					53	55	39	101	32	6	7	1	294
1/2						1	3	25	10		6	1	46
2/1								8	5		3		16
2/2								3	9	3	6	2	23
2/3									2		6		8
3/2													0
3/3											1		1
3/4													0
Total	2	21306	3546	2387	3382	1016	279	580	129	11	53	4	32695

SOURCE: Werner (1980).

markings or diffuse pulmonary fibrosis; 3.1 percent of the subjects had abnormal films, with a prevalence of 1.5 percent in nonsmokers and 4.4 percent in cigarette smokers. Dose–response relationships were present for the number of cigarettes smoked per day and for the duration of smoking. A second study evaluated 2,825 adults, again using 70 mm photofluorograms; this time interpretation was by readers other than the author, and the purpose of the evaluation was to examine the population for COLD rather than for interstitial fibrosis. The prevalence of diffuse interstitial fibrosis was 0.6 percent in nonsmokers and 2.1 percent in smokers.

Kilburn (1981) criticized these studies on the basis of their use of 70 mm films and the failure to use the ILO criteria for grading the roentgenographs. Epstein and colleagues (1984) applied the ILO criteria to 200 admission chest roentgenograms at an urban university medical center. Small opacities with profusions of 1/0 or greater were found in 22 (11 percent) of the subjects, none of whom had a documentable dust exposure or any known medical disease that caused interstitial lung disease. Of the 22, 12 (55 percent) were current or former cigarette smokers. Murphy and colleagues (1978) also used the ILO criteria in examining 68 shipfitters and pipefitters without known exposure to asbestos who were selected to serve as a control group for a study of similar workers with known exposure to asbestos. Of the control workers, 60 had chest roentgenograms classified as 0/1 or less, 6 (8.8 percent) had readings of 1/0 to 1/2, and 1 had a reading higher than 1/2. A previous study of the same group of workers (Murphy et al. 1972) had classified 14 percent of the controls as having slight abnormalities (1/0 to 1/2) and 2 percent as has having moderately advanced abnormalities (2/1 to 2/3). None of the control group were classified has having more advanced disease, and the results were not presented by smoking status.

In summary, the data suggest that a small percentage of chest roentgenograms of the general population may have changes that can be interpreted as interstitial fibrosis, and that slightly larger percentages of hospitalized patients and shipyard workers with no known asbestos exposure may have chest roentgenograms read as positive for interstitial fibrosis by the ILO criteria. Both the prevalence in these populations and the severity of the changes are far lower than those found in populations with significant asbestos exposures (Murphy et al. 1978), and they may reflect the sensitivity of the chest roentgenogram and the ILO classification to other causes of lung injury. The "dirty lung" described in smokers (Fraser and Pare 1979) may contribute to the smoking-related prevalence of "diffuse interstitial fibrosis" described by Weiss (1969) in the general population, but it is unlikely to be confused with the more advanced forms of fibrosis found in severe asbestos-related lung injury. However, the prevalence of changes in the general population,

particularly in the population of shipyard workers with no known asbestos exposure, suggests that classifying a mildly positive chest roentgenogram as asbestosis in the absence of a clear exposure history should require other confirming evidence of asbestos-induced lung injury. This caution may be particularly true for cigarette smokers.

Interstitial Fibrosis in Asbestos-Exposed Populations

As was mentioned earlier, cigarette smoking is not a competing cause of the diffuse severe interstitial fibrosis that occurs in some workers secondary to their inhalation of asbestos dust. However, modest peribronchiolar fibrosis (Cosio et al. 1978; Berend et al. 1979) and occasional fibrosis of respiratory bronchioles (Wright and Churg 1984) do occur as a response of the small airways to cigarette smoking, in addition to the periobronchiolar inflammation that is the predominant early response to cigarette smoking. These bronchioles are also the site of the early response to asbestos dust (Craighead et al. 1982), and therefore the threshold for radiologic perception of an abnormality may be crossed more frequently, or earlier, or at a lower dose of asbestos exposure in cigarette-smoking asbestos workers than in nonsmoking workers. In addition, the inflammatory response to cigarette smoke may enable or facilitate the fibrotic response to asbestos dust. Therefore, the question of a different exposure–response relationship between asbestos exposure and roentgenographic changes for smoking and nonsmoking asbestos workers should be considered.

Weiss (1984) recently reviewed the evidence relating cigarette smoking and roentgenographic fibrosis in asbestos-exposed populations. In Table 15, drawn from this review, is shown the prevalence of radiologic "asbestosis" in studies of asbestos-exposed populations. In general, the prevalence was higher in smokers than in nonsmokers; in several studies the difference was statistically significant. The highest prevalence ratios for smokers compared with nonsmokers are recorded in the populations with the lowest overall prevalence of roentgenographic fibrosis, and it is the studies where a high prevalence of disease is present that show similar rates of roentgenographic fibrosis among smokers and nonsmokers (if studies of populations of less than 100 are ignored). This observation is in part an obligatory result of the mathematics involved (a given difference in prevalence between smokers and nonsmokers produces a smaller prevalence ratio when there is a high prevalence than when there is a low prevalence), but it is also the effect that would be expected if the effect of smoking were a small independent risk of radiologic fibrosis or if the effect was to increase the frequency with which

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smoking asbestos workers cross the threshold for perception of roentgenologic abnormality.

The demonstration of an increased prevalence of roentgenographic changes interpreted as fibrosis in cigarette smokers does not establish that the changes are produced by smoking. As has been discussed earlier, cigarette smokers may have had a different cumulative asbestos exposure than nonsmokers in some of the populations studied. Liddell and colleagues (1982) examined the prevalence of roentgenographic fibrosis in a group of 515 asbestos miners born between 1891 and 1920 and found an increased prevalence of roentgenographic fibrosis with increasing age and cumulative asbestos exposure. Smokers and nonsmokers had similar prevalences of changes, but the smokers had marginally lower cumulative asbestos exposure. Harries and colleagues (1976) examined a younger population of shipyard workers with a lower prevalence of roentgenographic fibrosis (Table 16). The prevalence of changes was slightly higher in smokers than in nonsmokers, and seemed to increase in smokers after 10 to 14 years of asbestos exposure in comparison with after 20 to 24 years of asbestos exposure for nonsmokers. Dosage measures were not available for this study. Samet and colleagues (1979) examined a population of 383 asbestos workers with a prevalence of roentgenographic fibrosis (1/0 or greater) of 33.7 percent. They tested for interaction between smoking and asbestos exposure and found a small additive effect for roentgenographic changes, but no synergism between cigarette smoking and asbestos exposure. Rossiter and Berry (1978) examined the interaction of smoking and duration of asbestos exposure in a population with a lower prevalence of roentgenographic fibrosis and found a duration–response relationship for asbestos exposure only among cigarette smokers. The number of workers at risk in the nonsmoking category was small, however, making it difficult to determine whether the absence of a dose–response relationship in nonsmokers resulted from differences between smokers and non-smokers or was simply a reflection of the low rate of disease in the population.

In summary, cigarette smokers appear to have a higher prevalence of radiologic abnormality compatible with interstitial fibrosis than nonsmokers among populations of asbestos-exposed individuals with low prevalence of roentgenographic fibrosis (and presumably low levels of asbestos exposure). This difference is not apparent in populations with higher prevalences of roentgenographic fibrosis (and presumably higher asbestos exposures). One study (Harries et al. 1976) suggested that cigarette smokers develop an abnormal chest roentgenogram after a shorter duration of asbestos exposure than nonsmokers. There is little evidence to suggest that smokers develop more severe fibrosis (in contrast with a higher prevalence of fibrosis)

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TABLE 15.—Results of prevalence studies of the cigarette factor in asbestosis

Study	Smokers			Nonsmokers			Prevalence ratio[1]	95% confidence limits	
		Asbestosis			Asbestosis				
	Number	Number	Percent	Number	Number	Percent		Lower	Upper
Weiss (1971)	73	29	39.73	25	6	24.00	1.66	0.81	3.76
Langlands et al. (1971)	91	35	38.46	33	9	27.27	1.41	0.56	2.53
Harries et al. (1972)	1,635	49	3.00	808	20	2.48	1.21	0.72	2.03
Harries et al. (1976)	17,788	181	1.02	5,552	11	0.20	5.10	2.98	8.85
Weiss and Theodos (1978)									
Chrysotile	31	8	25.81	9	2	22.22	1.16	0.29	4.57
Chrysotile + amosite	38	26	42.11	10	0	0.00	∞	1.26[2]	56.31[2]
Hedenberg et al. (1978)	103	7	6.80	94	1	1.06	6.42	1.07	38.34
Rossiter and Harries (1979)	944	39	4.13	142	3	2.11	1.96	0.65	6.30
McMillan et al. (1980)	1,346	18	1.34	385	0	0.00	∞	1.09[2]	102.23[2]
Selikoff et al. (1980)	228	180	78.95	56	44	78.57	1.00	—	—
Pearle (1982)	99	9	9.09	32	1	3.13	2.90	0.43	20.06
Liddell (1982)	341	89	26.10	174	46	26.44	0.99	0.61	1.59

[1] Smokers to nonsmokers.

[2] Calculated by substituting 0.5 for 0 cases of pulmonary fibrosis in the nonsmoker group.

SOURCE: Weiss (1984).

TABLE 16.—Prevalence (percentage) of suspected or definite pulmonary fibrosis among 23,340 male in-yard British dockyard workers during 1972 and 1973, by smoking habit and duration of asbestos exposure

| Asbestos exposure (year) | Smoking habit | | | | | |
| | Nonsmokers | | Ex-smokers | | Smokers | |
	Number	With fibrosis (percent)	Number	With fibrosis (percent)	Number	With fibrosis (percent)
< 5	3,516	0.1	2,746	0.4	7,300	0.6
5–9	784	0.2	581	0.3	1,686	0.5
10–14	392	0.0	442	1.1	979	1.5
15–19	293	0.3	320	1.6	869	2.5
20–24	208	1.0	330	1.7	667	3.1
25–29	140	1.1	214	2.6	486	2.8
≥ 30	219	0.9	357	2.2	811	3.1
Total	5,552	0.2	4,990	0.8	12,798	1.1

SOURCE: Weiss (1984) (data derived from Harries et al (1976))

than nonsmokers. These data are consistent either with a small independent risk of interstitial fibrosis on chest roentgenogram produced by smoking (as suggested by the studies in non-asbestos-exposed populations) being added to the risk of fibrosis due to asbestos exposure or with the combination of asbestos-induced and smoking-induced changes in the small airways resulting in asbestos workers who smoke crossing the threshold for perceptible abnormality earlier than nonsmokers. However, it is clear that if cigarette smoking contributes to the development of interstitial fibrosis in asbestos-exposed workers, the contribution is a minor one in comparison with the effect of asbestos dust exposure.

Immunologic Response to Cigarette Smoke and Asbestos Dust

There is an extensive literature on both animal models and humans regarding alterations in the immune system following exposure to either asbestos or cigarette smoke; however, clinical and laboratory studies of combined exposure to asbestos and cigarette smoke are more limited.

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Humoral Immunity

Two independent studies (Kagan et al. 1977; Huuskonen et al. 1978) reported elevated polyclonal immunoglobulin (Ig) levels in populations of workers with asbestosis. Lange (1980) also correlated serum Ig levels with asbestosis. This study differentiated groups by sex and age, characteristics that can also affect the immune system. Cigarette smoking did not significantly correlate with serum Ig levels, whereas individuals with roentgenographically demonstrated asbestosis had increased levels of IgA and IgG. Asbestos workers, including those with interstitial fibrosis, were also evaluated for symptoms of chronic bronchitis. Male workers exhibiting symptoms for longer than 5 years had lower IgG and IgA values than asbestos workers without chronic bronchitis or with symptoms of bronchitis present for less than 5 years. Elevated IgA or IgM levels were found in a subgroup of male asbestos workers who were heavy smokers, as assessed by the duration of smoking multiplied by the average number of cigarettes smoked per day. The authors concluded that the asbestotic process and not the presence of chronic bronchitis was responsible for the high serum IgA and IgG levels (variable results have been reported regarding the level of serum IgA with chronic bronchitis) (Falk et al. 1970; Medici and Buergi 1971; Varpela et al. 1977). The immunoglobulin level alterations were found in workers with demonstrable lung disease. Therefore, it is unclear whether this alteration is involved in the pathogenesis of the disease or is an epiphenomenon, because the measurements were made when disease was already present.

Cellular Immunity

Wagner and colleagues (1979) evaluated factors affecting the peripheral blood leukocytes and T lymphocytes in 138 asbestos-exposed men. T lymphocyte subsets were identified by the ability of lymphocytes to rosette with erythrocytes, after incubation either for 1 1/2 hours (T helper cells) or overnight (T suppressor cells). Age, length of asbestos exposure, smoking history, evidence of roentgenographic fibrosis or pleural changes, and spirometric abnormalities were assessed. The smoking history in these asbestos-exposed workers was the factor that correlated best with lymphocyte changes. The group with roentgenographic changes of asbestosis and a history of smoking had an increased percentage in E-rosettes after 1 1/2 hours. This suggests an increase in the number of the T helper cells. Among workers with parenchymal chest roentgenographic changes, those who smoked had an increased number of the T helper cells compared with those who did not smoke. The number of T suppressor cells was not affected by the smoking history or by roentgenographic change.

Age and smoking as individual factors affecting lymphocyte percentage or number have also been assessed. There is some controversy about the effects on T lymphocytes. Silverman and colleagues (1975) showed no correlation between percentage of T lymphocytes and smoking or aging. Friedman and colleagues (1973) and Alexopoulos and Babitis (1976) did not demonstrate the effect of age on the percentage of T lymphocytes, but the absolute number of lymphocytes declined with age. Teasdale and colleagues (1976) and Smith and colleagues (1974) demonstrated a decline in the percentage and total number of T lymphocytes with age. Friedman and colleagues (1973) showed that the total number of leukocytes, including lymphocytes, increased in smokers until age 50, and then declined.

The effect of asbestos exposure on lymphocytes was studied by Kang and colleagues (1974) and by Kagan and colleagues (1977). The findings of both groups of investigators were similar. Kang and colleagues reported decreased erythrocyte-binding lymphocytes. Kagan and colleagues showed a decrease in percentage and in absolute number of T lymphocytes in a group of workers with asbestos exposure. Smoking as a contributing factor was not reported in these two studies.

More recently, these findings were substantiated by Miller and colleagues (1983) with the use of monoclonal antibody markers to differentiate T lymphocyte subsets. Smoking, length of asbestos exposure, and chest x-ray findings were evaluated. A decrease in percentage of T lymphocytes $(OK_{T(sub\ 3)}+)$ and in the suppressor subset of T lymphocytes $(OK_{T(sub\ 8)}+)$, with an increase in the ratio of helper T cells to suppressor cells $(OK_{T(sub\ 4)}-/OK_{T(sub\ 8)}+)$, was found in the group of 40 asbestos-exposed individuals compared with nonexposed individuals. Those with short asbestos exposure (less than 5 years) were similar to controls, and those with more than 5 years of exposure had the abnormalities. When assessing radiographic changes, those without chest roentgenographic changes had lymphocyte parameters similar to nonexposed individuals, those with pleural plaques had increased circulating helper cells $(OK_{T(sub\ 4)}+)$, and those with interstitial changes had decreased percentages of T lymphocytes $(OK_{T(sub\ 3)}+)$ and suppressor cells $(OK_{T(sub\ 8)}+)$ and an increased ratio of helper to suppressor cells $(OK_{T(sub\ 4)}+/OK_{T(sub\ 8)}+)$. Smoking habit did not influence these results. Miller and colleagues (1983) theorized several possibilities to explain the findings. The asbestos exposure may initially stimulate the immune system, accounting for the increase in the helper cells in subjects with pleural plaques. There may be an isolated toxic effect to suppressor cells affecting the percentage of this subset, and thus the total percentage of T lymphocytes. Lymphocytes may be distributed in organs (i.e., the lung) once fibers are inhaled, and thus the peripheral

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blood lymphocyte parameters are altered. Although the differences are most striking in subjects with roentgenographic changes, the lymphocyte alterations may not be related to the pathogenesis of these changes, but may be a secondary change due to chronic disease.

In other studies (Ginns et al. 1982; Miller et al. 1982), smoking was also found to cause T lymphocyte subset changes. These changes were found in heavy smokers (50 to 120 pack-years) and not in light to moderate smokers (10 to 49 pack-years). Heavy smokers had increased total T lymphocytes (OK_{T3^+}), a decreased percentage of T helper cells (OK_{T4^+}), an increased total number of T suppressor cells (OK_{T8^+}), and a decreased ratio of helper to suppressor cells.

De Shazo and colleagues (1983) also examined lymphocyte subsets in 31 current and former asbestos-cement workers compared with 52 healthy controls after adjustments had been made for possible confounding effects of age, race, and smoking. The asbestos workers had significantly decreased percentages and numbers of B and T lymphocytes in the peripheral blood. Analysis of T lymphocyte subpopulations revealed that total T cell numbers (OK_{T3^+}) and helper-inducer T cell numbers (OK_{T8^+}) were decreased by similar proportions. These decreases were negatively correlated with time since the end of exposure to asbestos. In both workers and controls, lymphocyte proliferative response to phytohemagglutinin was correlated positively with the number of (OK_{T4^+}) cells and negatively with age. No relationship was detected between any of the immunologic aberrations noted in the workers and the radiographic category of pneumoconiosis, estimates of cumulative asbestos exposure, or abnormalities of pulmonary function.

Lymphocyte function was assessed by Campbell and colleagues (1980) by the mitogen lymphocyte transformation response of peripheral blood lymphocytes. Allowing for the decline in response seen with increasing age, there was an increase in response to phytohemagglutinin (PHA) and pokeweed mitogen (PWM) in asbestos workers who smoked compared with ex-smokers and nonsmokers. These findings were in agreement with those reported by Haslam and colleagues (1978).

Sister Chromatid Exchange Frequency

An in vitro cytogenetic assay, sister chromatid exchange (SCE) frequency, has been utilized to demonstrate chromosomal breakage in different mammalian cell lines following exposure to asbestos. In a study reported by Rom and colleagues (1983), 25 asbestos insulators had a small increase in frequency of SCE in peripheral blood lymphocytes compared with controls. The SCE rate increased slightly with increasing years of exposure to asbestos, when age and smoking were controlled. Smokers had similar rates of occurrence of SCE among both controls and asbestos workers. In nonsmokers,

those with asbestos exposure had a significantly increased SCE rate compared with controls. Butler (1980) and Crossen and Morgan (1980) did not detect a difference in SCE frequency.

Public Health Implications

The data are unequivocal that cigarette smoking and asbestos exposure have produced substantial death and disability. The residual public health questions generated by these data focus on how to reduce the future risk of illness and death. As asbestos exposures are reduced, clinically disabling interstitial fibrosis should become a rare phenomenon in workers currently beginning their work careers. As asbestos exposures are reduced, it will become increasingly difficult to identify an increase in lung cancer death rates among asbestos workers that is greater than those of the general population. While the risk of developing mesothelioma is not associated with smoking, the risk of developing mesothelioma should be reduced by the lower exposure levels that currently exist, but persists even at very low levels of exposure. A reduction in the current U.S. standard (2f/cc) is being considered; once adequate asbestos dust controls are applied and enforced, future gains in reducing asbestos exposure are likely to come from reducing the exposure of workers employed in jobs other than asbestos mining and manufacturing. These jobs include construction workers who may be exposed during the demolition or remodeling of existing structures constructed with asbestos materials, and maintenance workers who may be similarly exposed to existing asbestos-containing materials. Current concerns are the risk involved in removing asbestos from existing buildings in order to reduce environmental contamination and the need to educate the workers involved in these tasks to prevent their exposure as they remove these materials.

Unfortunately, little can be done to reduce the current asbestos burden in workers exposed prior to the introduction of environmental controls. For these workers, it is clear that the single most important intervention that would alter their future disease risk is the cessation of cigarette smoking. The elimination of cigarette smoking in this population would not only substantially reduce the number of future lung cancer deaths but also moderate the contribution of cigarette-induced COLD to the restrictive ventilatory limitation that may develop in these workers. The issues of liability and responsibility for the disease that is occurring in these workers will continue to be argued for an extended period of time, but these arguments should not confuse or impede the efforts to alter the future disease risk in these workers. The goal is not, and should not be, to eliminate only that disease burden attributable to future asbestos exposure, but rather to reduce as much as possible, by any

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means possible, the enormous risk of death and disability that currently exists for these workers. Smoking cessation is therefore an intrinsic and essential part of any effort to reduce asbestos-related disease and disability.

Summary and Conclusions

1. Asbestos exposure can increase the risk of developing lung cancer in both cigarette smokers and nonsmokers. The risk in cigarette-smoking asbestos workers is greater than the sum of the risks of the independent exposures, and is approximated by multiplying the risks of the separate exposures.
2. The risk of developing lung cancer in asbestos workers increases with increasing number of cigarettes smoked per day and increasing cumulative asbestos exposure.
3. The risk of developing lung cancer declines in asbestos workers who stop smoking when compared with asbestos workers who continue to smoke. Cessation of asbestos exposure may result in a lower risk of developing lung cancer than continued exposure, but the risk of developing lung cancer appears to remain significantly elevated even 25 years after cessation of exposure.
4. Cigarette smoking and asbestos exposure appear to have an independent and additive effect on lung function decline. Nonsmoking asbestos workers have decreased total lung capacities (restrictive disease). Cigarette-smoking asbestos workers develop both restrictive lung disease and chronic obstructive lung disease (as defined by an abnormal FEV_1/FVC), but the evidence does not suggest that cigarette-smoking asbestos workers have a lower FEV_1/FVC than would be expected from their smoking habits alone.
5. Both cigarette smoking and asbestos exposure result in an increased resistance to airflow in the small airways. In the absence of cigarette smoking, this increased resistance in the small airways does not appear to result in obstruction on standard spirometry as measured by FEV_1/FVC.
6. Asbestos exposure is the predominant cause of interstitial fibrosis in populations with substantial asbestos exposure. Cigarette smokers do have a slightly higher prevalence of chest radiographs interpreted as interstitial fibrosis than nonsmokers, but neither the frequency of these changes nor the severity of the changes approach levels found in populations with substantial asbestos exposure.
7. The promotion of smoking cessation should be an intrinsic part of efforts to control asbestos-related death and disability.

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